IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.:	10/079,931
Applicants:	Kuijpers et al.
Filed:	February 19, 2002
Title:	TREATMENT OF OCULAR DISORDERS
TC/A.U.:	1644
Examiner:	Nolan, Patrick
Confirmation No.:	7525
Docket No.:	294-70 CON/RCE
Dated:	

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

I, ROBERTUS WILHELMUS KUIJPERS, M.D., Ph.D., 311 Heemraadssingel, 3023 BR Rotterdam, declare as follows:

1. I am an expert in the field of Ophthalmic Immunology as evidenced by my resume, which is attached as Exhibit A. Additionally, I am one of the inventors of the above-identified U.S. Patent application, filed on February 19, 2002, which is a continuation application of U.S.S.N.: 09/258,240, filed February 26, 1999.

2. The action of somatostatins (*i.e.* somatostatin analogues) is biochemically different from the action of tyrosine kinase inhibitors.

3. Somatostatin analogues act directly on retinal cells. Somatostatin receptors are coupled to G proteins in the cell membrane, and generate a transmembrane signal after binding of somatostatin analogues. Depending on the cell types, somatostatin receptors are coupled to a diversity of signal transduction pathways. Various signalling proteins, including adenylate cyclase, guanylate cyclase, phospholipase C, phospholipase A2, potassium, and calcium channels, Na+/H+ exchanger, Src, Erk1/2 and p38 mitogen-activated protein (MAP) kinases

and tyrosine phosphatases have been reported.

4. The action of tyrosine kinase inhibitors involves inhibition of phosphorylation and activation of effector proteins. Many polypeptide growth factors activate cells through membrane receptors with cytoplasmatic tyrosine kinase activity. The effect depends on the type of receptor and the type of tyrosine kinase that are involved. There are many types tyrosine kinases.

5. I have read and understood U.S. Patent No. 6,028,099 in the way that although all possible Tyr-kinase inhibitors with the basic chemical structure which is shown in claim 1 of the patent could be used, in fact the work has been done using the protein kinase pathway inhibitor genistein. Genistein is a phytoestrogen that can be found in soy products and binds preferentially to estrogen receptor beta. The patent is focused on protein kinase inhibitors and inhibition of neovascularization which, in my understanding, may mean vascular endothelial growth factor (VEGF)-receptor coupled tyrosine kinase inhibition.

6. Since the action of somatostatin analogues is different from the action of tyrosine kinase inhibitors, the compounds are used separately from each other. To the best of my knowledge, no cumulative action, nor synergistic action, of these two compounds has been described in the treatment of retina diseases.

7. Somatosatin analogues have been used for more than 15 years and have been proven to be safe drugs.

8. Tyrosine kinase inhibitors are not yet on the market, or only recently introduced on the market. Tyrosine kinase inhibitors have been described with a significant pattern of side-effect.

9. It is likely that when one uses two active compounds together (instead of just one active compound) more side effects may occur.

10. I believe that a somatostatin analogue administered *without* a kinase inhibitor provides a safer clinical profile than a somatostatin analogue administered *with* a kinase inhibitor.

11. In one embodiment, the instant invention includes a method for treating an ocular disorder by administering a somatostatin analogue (e.g., octreotide and lanreotide) to a patient. The somatostatin analogue binds to at least one somatostatin receptor in the eye.

12. The ocular disorders treatable by this method include retinal edema, macular edema, cystoid macular edema, age related macular degeneration, diabetic retinopathy, and central serous chorio-retinopathy.

13. Topical administration of a somatostatin analogue is effective in treating the aforementioned ocular disorders. Further experimental results will follow.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that those statements were made with the knowledge that willfully false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willfully false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: _____ _____

Robertus Wilhelmus Kuijpers, MD

222170

EXHIBIT A

CV.
Robert W.A.M. Kuijpers
Born 20-09-1958

Education:

MD Rijks Universiteit Leiden	1986
PhD "neonatal alloimmune cytopenias" Universiteit van Amsterdam	1992
Clinical training Ophthalmology Academisch Ziekenhuis Maastricht	1991-1995
Diplome European Board of ophthalmology	1995

Scientist and head of Laboratory for leukocyte serology Centraal Laboratorium voor de Bloedtransfusiedienst (CLB) and Laboratory for experimental immunology, Universiteit van Amsterdam	1989-1991
Stafmember University eye clinic, Academisch Ziekenhuis Rotterdam	from 1995

Member American Academy of Opthalmology (AA)
Member American Organistion for Research in Visual Science and Ophthalmology (ARVO)

Publications:

Kuijpers RWA. Faber NM, Kanhai HH, Von dem Borne AE. Typing of fetal platelet alloantigens when platelets are not available. Lancet 336 (8726):1319, 1990

Huizinga TW, Kuijpers RWA, Kleijer M, Schulpen TW, Cuypers HT, Roos D, Von dem Borne AE. Maternal genomic neutrophil FcRIII deficiency leading to neonatal isoimmune neutropenia. Blood 76 (10):1927, 1990

Von dem Borne AE, Ouwehand WH, Kuijpers RWA. Theoretic and practical aspects of platelet crossmatching. Transfusion Medicine Reviews 4 (4):265, 1990

Mackhorst DG, Hack WW de Waal FC, Kuijpers RWA. A child with neonatal allo-immune neutropenia. Tijdschrift voor Kindergeneeskunde. 58 (5):175, 1990

Kuijpers RWA, Dooren MC, Von dem Borne AE, Ouwehand WH. Detection of human monocyte-reactive alloantibodies by flow cytometry after selective downmodulation of the Fc receptor I. Blood 78 (8):2150, 1991

Kuijpers RWA, Faber NM, Cuypers HT, Ouwehand WH, Von dem Borne AE. NH2-terminal globular domain of human platelet glycoprotein Ib alpha has a methionine 145/threonine 145 amino acid polymorphism, which is associated with the HPA-2 (Ko) alloantigens. Journal of Clinical Investigation 89 (2):581, 1992

Kuijpers RWA, Von dem Borne AE, Kiefel V, Eckhhardt CM, Waters AH, Zupanska B, Barz D, Taaning E, Termijtelen A, Ouwehand WH. Leucine33-proline33 substitution in human platelet glycoprotein IIIa determines HLA-DRw52a (Dw24) association of the immune response against HPA-1a (Zwa/PlA1) and HPA-1b (Zwb/PlA2). Human Immunology 34 (4):253, 1992

Dooren MC, Kuijpers RWA, Joekes EC, Huiskes E, Goldschmeding R, Overbeeke MA, Von dem Borne AE, Engelfriet CP, Ouwehand WH. Protection against immune haemolytic disease of newborn infants by maternal monocyte-reactive IgG alloantibodies (anti-HLA-DR). Lancet 339 (8801):1067, 1992

Kuijpers RWA, Ouwehand WH, Bleeker PM, Christie D, Von dem Borne AE. Localization of the platelet-specific HPA-2 (Ko) alloantigens on the N-terminal globular fragement of platelet glycoprotein Ib alpha. Blood 79 (1):283, 1992

Kuijpers RWA, Ouwehand WH, Peelen W, Michiels JJ, Engelfriet CP, Von dem Borne AE. Thrombocytopenia due to platelet glycoprotein IIb/IIIa reactive autoantibodies non-reactive with platelets from EDTA blood. Vox Sanguinis 63 (2):119, 1992

Kuijpers RWA, Simsek S, Faber NM, Godschmeding R, Van Wermeskerken RK, Von dem Borne AE. Single point mutation in human glycoprotein IIIa is associated with a new platelet-specific alloantigen (Mo) involved in neonatal alloimmune thrombocytopenia. Blood 81 (1):70, 1993

Schreij G, Kuijpers RWA, Pijpers E, Beintema MR. Unusual ocular symptoms and signs associated with infectious mononucleosis. Lancet 344 (8932):1302, 1994

Kuijpers RWA, Van den Anker JN, Baerts W, Von dem Borne AE. A case of severe neonatal thrombocytopenia with schizencephaly associated with anti-HPA-1b and anti-HPA-2a. British Journal of Haematology 87 (3):576, 1994

Simsek S, Vlekke AB, Kuijpers RWA, Goldschmeding R, Von dem Borne AE. A new private platelet antigen, Gro-a, localized on glycoprotein IIIa, involved in neonatal alloimmune thrombocytopenia. Vox sanguinis 67 (3):302, 1994

La Heij E, Kuijpers RWA, Baarsma S, Kijlstra A, Mooij CM. Integrin expression on histological specimen of iris-biopsies in Fuchs iridocyclitis.
British Journal op Ophthalmology, 82(4):432, 1998

Kuijpers RWA, Baarsma S, Van Hagen CM. Treatment of cystoid macular edema with octreotide.
New England Journal of Medicine, 338 (9):624, 1998

Dooren MC, Ouwehand WH, Verhoeven AJ, Von dem Borne AEGKr, Kuijpers RWA. Adult respiratory distress syndrome after experimental intravenous γ-globulin concentrate and monocyte-reactive IgG antibodies. Lancet 352(9140):1601, 1998

Kuijpers RWAM, Vingerling JR. Zakboek ooghcelkunde. Maarsen, 1999; Elsevier / Bunge

van Hagen PM, Baarsma GS, Mooy CM, Ercoskan EM, ter Averst E, Hofland LJ, Lamberts SW, Kuijpers RW.
Somatostatin and somatostatin receptors in retinal diseases.
Eur J Endocrinol. 2000 Oct;143 Suppl 1:S43-51. No abstract available.

Lambooij AC, Kliffen M, Kuijpers RW, Houtsmuller AB, Broerse JJ, Mooy CM.
Apoptosis is present in the primate macula at all ages.
Graefes Arch Clin Exp Ophthalmol. 2000 Jun;238(6):508-14.

Lambooij AC, Kuijpers RW, van Lichtenauer-Kaligis EG, Kliffen M, Baarsma GS, van Hagen PM, Mooy CM.
Somatostatin receptor 2A expression in choroidal neovascularization secondary to age-related macular degeneration.
Invest Ophthalmol Vis Sci. 2000 Jul;41(8):2329-35.